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# Journal club

## THERE'S MORE TO LITHIUM THAN NIRVANA

Some of the most widely prescribed drugs are poorly understood in terms of their mechanism of action. Perhaps the simplest drug in our pharmacopeia is lithium, which Nirvana named a song after in 1990. More importantly, lithium is widely used in the treatment of bipolar disorder. In 1996, there was no lack of explanations of how lithium worked to stabilize mood. Indeed, the drug was implicated in multiple cellular processes, including G protein signalling and inositide metabolism. Given that the effective clinical concentration of lithium in blood is close to 1 mM, the ion probably has pleiotropic actions. At the time, evidence suggested that lithium causes the depletion of cellular inositol by blocking the activity of inositol monophosphatase (IMPase), an enzyme that might have a role in bipolar disorder. However, when Klein and Melton tested a potent new IMPase inhibitor in 1996, it failed to phenocopy the biological effects of lithium on development. Instead, they presciently noted that the lithium treatment of *Xenopus laevis* embryos or *Dictyostelium discoideum* yielded effects similar to those that had been recently described for dominant-negative glycogen synthase kinase 3β (gsk3β) mutants or the gene inactivation of *gsk3b*, respectively.

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Klein and Melton then demonstrated that GSK3β was a lithium target *in vitro*. Although the concentration for 50% inhibition was rather unimpressive at 2 mM, they demonstrated that the ion had no effect on a collection of other kinases and pointed out that 2 mM was close to the clinically relevant dose. Later, in 2004, Klein's group showed that mice mutant for one *Gsk3b* allele displayed behaviour that was similar to wild-type animals treated with lithium. The original link between GSK3β and lithium found in 1996 opened up the field for the investigation of the effects of GSK3 on neuropsychology. Although definitive proof that GSK3 inhibition directly contributes to the effects of lithium in patients is still lacking, multiple roles for this kinase in brain function and behaviour are beyond question. The important clue here was gleaned from the conservation of a phenotype across species, which gives us a crucial biological lesson.

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